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Synthesis of (±)-*E*-4-(1,2,4-Trihydroxy-2,6,6-trimethylcyclohexyl)-but-3-en-2-one: A Novel Degraded Carotenoid Isolated from New Zealand Thyme (*Thymus vulgaris*) Honey

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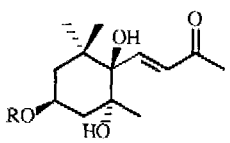
Keywords: Degraded carotenoid; synthesis; stereoselective; honey; *Thymus vulgaris*

Abstract: A racemic synthesis of the title compound is described starting from β-ionone. The key steps involve selective hydroboration of a triene, followed by molybdenum mediated epoxidation of the resulting homoallylic alcohol with subsequent ring opening of the epoxide to give the title compound.

As part of a continuing investigation into the role of the non-carbohydrate extractives of New Zealand honeys as floral source markers,[1] the novel degraded carotenoid **1a** was isolated chromatographically and identified by a combination of MS, NMR and crystallography.[2] Currently, floral source must be proven by the tedious procedure of counting pollen grains, hence the interest in developing comparatively rapid GC based analyses of the non-carbohydrate extractives of honeys.[1] The triol **1a** has been shown to be unique to honey from Thyme (*Thymus vulgaris*) and hence may serve as proof of floral source for this honey.



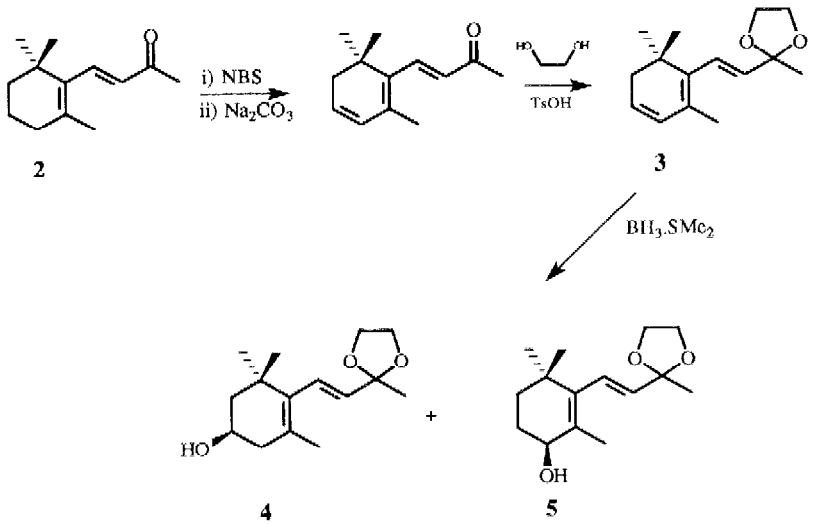
1a R = H
1b R = Ac

Although **1a** crystallised in the optically active space group $P2_12_12_1$, it was not possible to determine the absolute configuration from the crystallographic data. To assist with the determination of the absolute stereochemistry of the natural product and to help identify the source of the triol (i.e. whether it arose directly from a degraded carotenoid present in the flower, or by chemical modification of a carotenoid during or after transport to the hive by the bees) an enantioselective synthesis of **1a** is being developed. In this connection, a convenient racemic synthesis has been developed, and is the

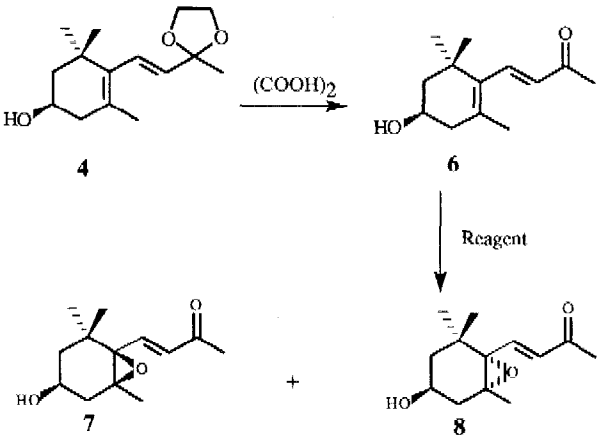
subject of this communication.

In an excellent demonstration of the utility of Brown's asymmetric hydroboration protocol,[3] chiral precursors of both enantiomers of **1b** were synthesised by Rüttiman *et al.*[4] and both (+)- and (-)-**1b** were used as key intermediates in the total syntheses of a range of carotenoids containing trihydroxy-substituted end groups.[5] However, the synthetic method required a starting material which was not readily available, and herein we describe a synthesis based around commercially available β-ionone **2**.

Treatment of **2** with N-bromosuccinimide/base[6] followed by protection of the ketone as a 1,3-dioxolane[7] afforded the dehydro- derivative **3**.[8] Hydroboration of **3** to the homoallylic alcohol **4** using $(Ipc)_2BH$,[3] with the intention of achieving asymmetric induction, was unsuccessful in our hands; the reaction gave a mixture of products, with only a low yield of **4**. However, treatment of **3** with $BH_3.SMe_2$[9] resulted in a reasonable regioselectivity for the terminal alkene of the triene system, with a 3:1 mixture of **4** and **5** being isolated in a yield of 32%.[10]



Deprotection of **4** with oxalic acid[11] to give the corresponding ketone **6**, followed by epoxidation of **6** with *m*-chloroperbenzoic acid[5] afforded a 75:25 mixture of **7** and **8** in high yield. However, the epoxides were not readily separated chromatographically, and this method was discarded. The selectivity of the epoxidation step is critical if chirality is to be introduced by kinetic resolution of the alcohol **4**.[12] In this case it was found that the $Mo(CO)_6$/t-BuOOH procedure of Sharpless[13] utilising the directing effect of the homoallylic alcohol gave the required degree of selectivity in the epoxidation step.



Reagent	7	8
MCPBA	75	25
$Mo(CO)_6$/t-BuOOH	>98	<2

Treatment of **7** with a catalytic amount of 30% H_2SO_4[5] afforded a stereospecific opening of the epoxide to generate **1a**. The reaction proceeded with nett retention of configuration at C1, and the racemic triol was found to have the same NMR and MS data as the natural product,[2] although as a racemic mixture it had a different melting point.[14] Further work is[12] is continuing with a view to developing an enantioselective enzyme-mediated kinetic resolution the homoallylic alcohol **6** to enable synthesis of both enantiomers of the title compound.

REFERENCES AND NOTES

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2. Tan, S.T.; Wilkins, A.L.; Holland, P.T. *Aust. J. Chem.* **1989**, *42*, 1799-804.
3. Brown, H.C.; Yoon, N.M. *Israel J. Chem.* **1976/77**, *15*, 12-16.
4. Rüttimann, A.; Mayer, H. *Helv. Chim. Acta* **1980**, *63*, 1456-1462.
5. Buchecker, R.; Marti, U.; Eugster, C.H. *Helv. Chim. Acta* **1984**, *67*, 2043-2056.
6. Findlay, J.A.; Mackay, W.D. *Can. J. Chem.* **1971**, *49*, 2369-2371.
7. Greene, T.W. *Protective Groups in Organic Synthesis*; Wiley: New York. 1981, p124.
8. Spectral data for **3**:
   ^{1}H NMR (300 MHz) δ: 0.98(6H,s, C-6Me), 1.52(3H, s, 1'-CH_3), 1.79(3H, s, 2-CH_3), 2.05(2H, dd, $J_{5,4}$ = 4.3Hz, $J_{5,3}$ = 1.6Hz, H5$_a$/H5$_b$), 3.95(4H, m, 2 x CH_2O)), 5.47(1H, d, $J_{3'4'}$ = 16.1Hz, H3'), 5.70(1H, dt, $J_{4,3}$ = 9.5Hz, $J_{4,5a}$ = 4.3Hz, $J_{4,5b}$ = 4.3Hz, H4), 5.80(1H, dt, $J_{3,4}$ = 9.5Hz, $J_{3,5a}$ = 1.6Hz, $J_{3,5b}$ = 1.6Hz, H3), 6.21(1H, d, $J_{4,3'}$ = 16.1Hz, H4').

^{13}C NMR (75.5MHz) δ: 19.76(q, C-2Me), 25.31(q, C-1'), 26.52(q, C-6Me), 33.65(s, C 6), 39.55(t, C-5), 64.49(t, (CH2O)2), 107.68(s, C-2'), 124.90(d, C-4), 126.22(s, C-2), 127.04(d, C-4'), 129.38(d, C-3), 133.23(d, C-3'),and 137.15(s, C-1).

M.S. m/z: $M^{+\cdot}$: 234(40), $M^{+\cdot}$-CH_3: 219(76), 147(29), 119(22), 87(100), 73(31). Found: m/z 234.1629. $C_{15}H_{22}O_2$ requires m/z 234.1619.

9. Brown, H.C.; Desai, M.C.; Jadhav, P.K. *J. Org. Chem.* **1982**, *47*, 5065-5069.

10. Spectral data for **4**:
^{1}H NMR (300MHz) δ: 1.02 (3H, s, 6-CH_3), 1.05(3H,s, 6-CH_3), 1.44(1H, t, $J_{5a,4}$ = 12.0Hz, $J_{5a,5b}$ = 12.0Hz, $H5_a$), 1.51(3H, s, 1'-CH_3), 1.67(3H,s, 2-CH_3), 1.75(1H, ddd, $J_{5b,5a}$ = 12.0Hz, $J_{5b,4}$ = 3.6Hz, $J_{5b,3b}$ = 1.6Hz, $H5_b$), 1.98(1H, dddd, $J_{3a,3b}$ = 16.7Hz, $J_{3a,4}$ = 9.6Hz, $J_{3a,4'}$ = 2.5Hz, $J_{3a,C\text{-}2Me}$ = 1.22Hz, $H3_a$), 2.34(1H, ddt, $J_{3b,3a}$ = 16.7Hz, $J_{3b,4}$ = 5.6Hz, $J_{3b,C\text{-}2Me}$ = 1.6Hz and $J_{3b,5b}$ = 1.6Hz, $H3_b$), 3.92(5H, m, 4-H and 2 x CH_2O), 5.35(1H, d, $J_{3',4'}$ = 16.1Hz, H3'), and 6.15(1H, ddt, $J_{4',3'}$ = 16.1Hz, $J_{4',3a}$ = 2.5Hz, $J_{4',3b}$ = 1.2Hz and $J_{4',C\text{-}2Me}$ =1.2Hz, H4').
^{13}C NMR (75.5MHz) δ: 21.2(q, 2-CH_3), 25.2(q, C1'), 28.4(q, 6-CH_3), 30.1(q, 6-CH_3), 36.7(s, C6), 42.1(t, C3), 48.1(t, C5), 64.5(t, 2 x CH_2O), 65.0(d, C4), 107.5(s, C2'), 125.8(s, C1 or C2), 127.4(d, C4'), 134.3(d, C3'), 136.5(s, C2 or C1).
M.S. m/z: $M^{+\cdot}$: 252(9), $M^{+\cdot}$-Me: 237(53), M-Me-H_2O 219(35), 175(19), 87(100). Found: m/z 252.1713. $C_{15}H_{24}O_3$ requires m/z 252.1752.

11. Ref. 7, p127.

12. Work is in progress on the development of an enzymatic resolution of cyclohexanols where the stereodifferentiating groups are remote from the centre of chirality, where, unlike 2-substituted cyclohexanols (see e.g. Hoenig, H.; Seufer-Wasserthal, P. *Synthesis* **1990**, 1137-1140), a satisfactory method has yet to be developed. Details of this study will be published separately.

13. Sharpless, K.B.; Michaelson, R.C. *J. Am. Chem. Soc.* **1973**, *95*, 6136-6137.

14. Data for **1a**: White crystals, m.p. 151-152°C.
^{1}H NMR (300MHz) δ: 0.87(3H, s, 6-CH_3), 1.18(3H, s, 2-CH_3), 1.28(3H, s, 6-CH_3), 1.59(5H, m, $H5_a$/$H5_b$ and 3 x OH), 1.81(1H, dd, $J_{3a,3b}$ = 13.1Hz, $J_{3a,4}$ = 10.8Hz, $H3_a$), 1.88(1H, ddd, $J_{3b,3a}$ =-13.1Hz, $J_{3b,4}$ = 4.6Hz, and $J_{3b,5b}$ = 1.8Hz, $H3_b$), 2.32(3H, s, H1'), 4.18(1H, m, H4), 6.37(1H, d, $J_{3',4'}$ = 16.2Hz, H3'), 7.25(1H, d, $J_{4',3'}$ = 16.2Hz, H4').
^{13}C NMR (75.5Mz) δ: 25.6(q,), 26.6(q), 27.6(q, 6-CH_3), 27.8(q, 6-CH_3), 40.3(t), 45.5(s,C6), 45.6(t), 64.3(d,C4), 77.1(s, C1 or C2), 78.5(s, C2 or C1), 131.3(d, C4'), 148.5(d, C3'), 198.2(s, C1').
M.S. m/z $M^{+\cdot}$-H_2O 224(38), 181(28), 125(100), 99(80). Found : m/z 224.1379, $C_{15}H_{20}O_3$ ($M^{+\cdot}$-H_2O) requires m/z 224.1412.

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